Armed Forces College of Medicine

AFCM

Glucose Homeostasis-1

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Lecturer

Medical Biochemistry and molecular biology

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. **Discuss the basic strategy of metabolism and metabolic regulation**
2. **Outline sources of blood glucose.**
3. **Outline hormonal regulation of metabolic pathways**
4. **Categorize the metabolic effects and regulators of Insulin and glucagon Release**

Lectures outlines

- basic strategy of metabolism
- Metabolic Regulation
- Glucose Hemostasis
- Endocrine Regulation Of Metabolism
- #Overview of the Post Absorptive State
- #Fasting state

•Basic strategy of metabolism

Metabolism Consist of Highly Interconnected Pathways

- The basic strategy of metabolism is to form ATP, NADPH, and building blocks for biosyntheses.

. *ATP is the universal currency of energy*

Energy source in muscle contraction, active transport, signal amplification, and biosyntheses.

1. ***ATP is generated by the oxidation of fuel molecules such as glucose, fatty acids, and amino acids.***

The common intermediate in most of these oxidations is acetyl CoA.

The carbon atoms of the acetyl unit are completely oxidized to CO_2 by the TCA with the concomitant formation of NADH and FADH2.

These electron carriers then transfer their high potential electrons to the respiratory chain.

2. *NADPH is the major electron donor in reductive biosyntheses.*

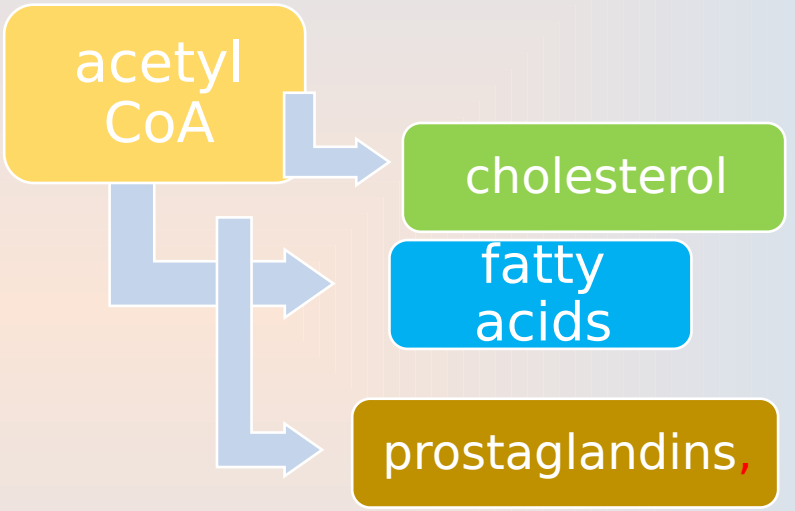
In most biosyntheses, the products are more reduced than the precursors, and so reductive power is needed as well as ATP.

The high-potential electrons required to drive these reactions are usually provided by NADPH.

The pentose phosphate pathway supplies much of the required NADPH.

3. ***Biomolecules are constructed from a small set of building blocks***

The metabolic pathways that generate ATP and NADPH also provide building blocks for the biosynthesis of more-complex molecules.



MCQs

- The common intermediate in most of oxidations reaction for production of Atp is -----

- acetyl CoA

Metabolic Regulation

Metabolic Regulation

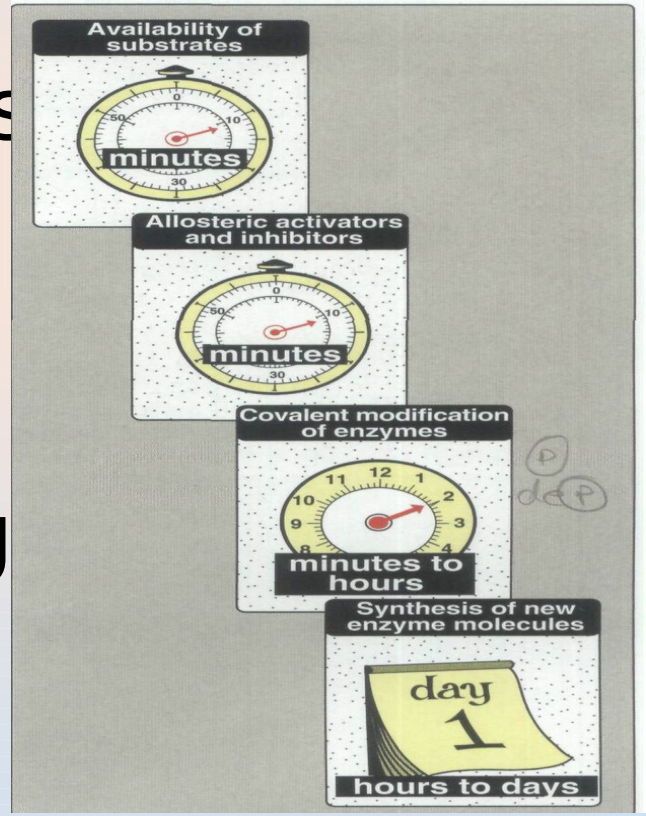
Anabolism and catabolism must be precisely coordinated

1. *Allosteric interactions*

Enzymes that catalyze essentially irrevers
reactions are likely control sites,

and the first irreversible reaction in a
pathway

(the committed step) is nearly always tig
controlled.



2. Covalent modification

Some regulatory enzymes are controlled by covalent modification in addition to allosteric interactions.

For example, the catalytic activity of glycogen phosphorylase is enhanced by phosphorylation, whereas that of glycogen synthase is diminished.

3. Enzyme levels

The amounts of enzymes, as well as their activities, are controlled.

The rates of synthesis and degradation of many regulatory enzymes are altered by hormones.

4.Avaiability of substrates

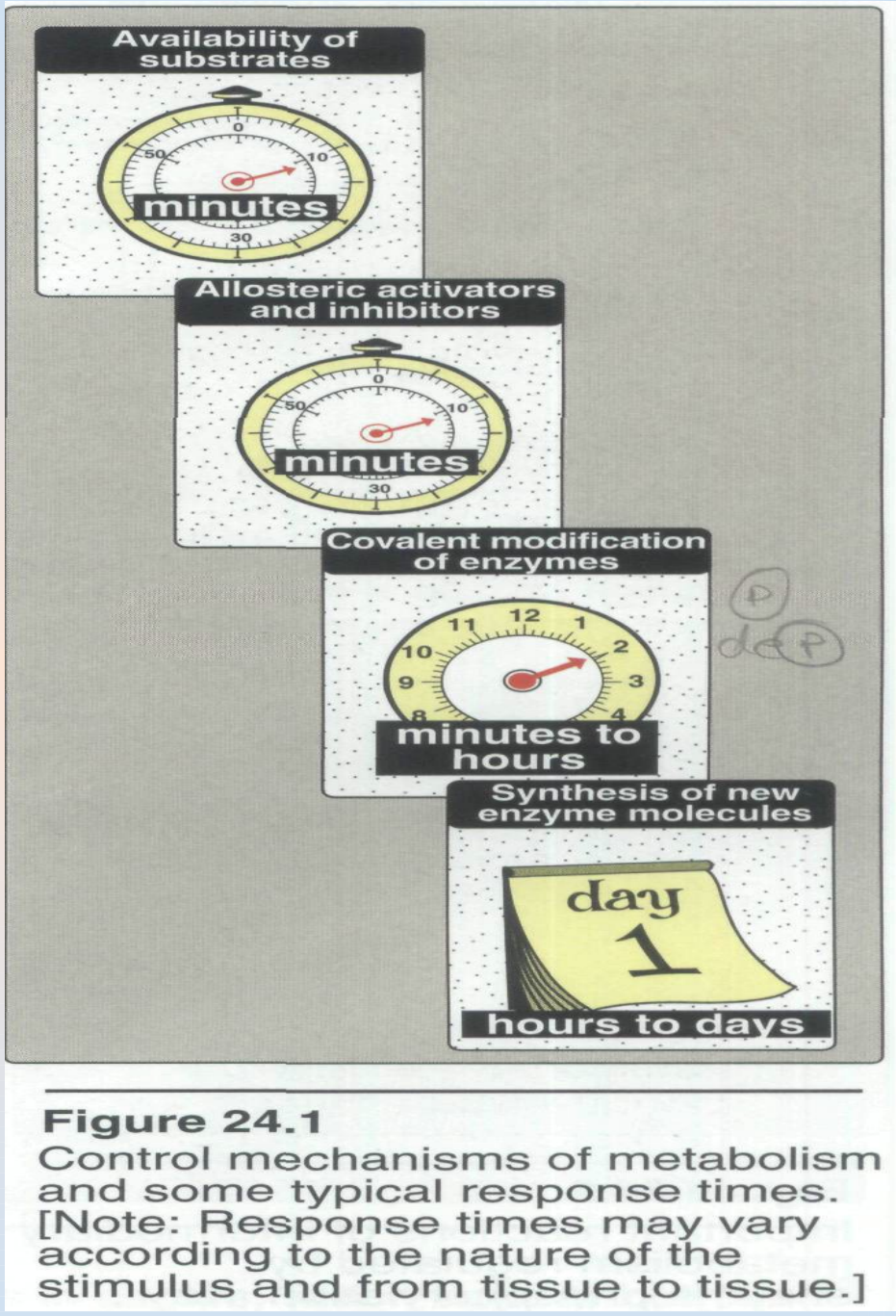


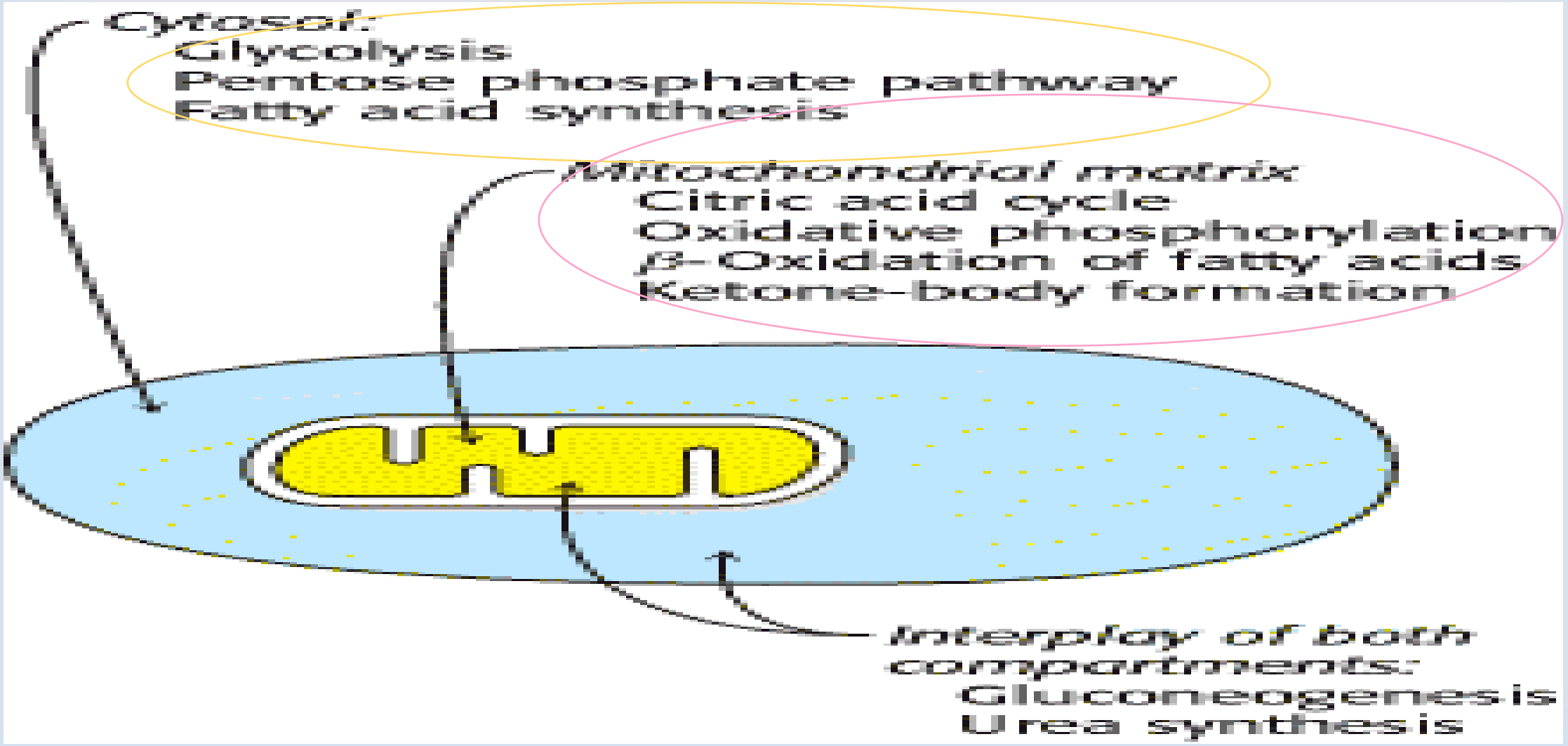
Figure 24.1
Control mechanisms of metabolism and some typical response times. [Note: Response times may vary according to the nature of the stimulus and from tissue to tissue.]

5. Compartmentation

The metabolic patterns of eukaryotic cells are markedly affected by the presence of compartments.

The fates of certain molecules depend on whether they are in the cytosol or in mitochondria, and so their flow across the inner mitochondrial membrane is often regulated.

Compartmentation of the Major Pathways of Metabolism



6. Metabolic specializations of organs. *Regulation in higher eukaryotes is enhanced by the existence of organs with* different metabolic roles.

Metabolic specialization is the result of differential gene expression.

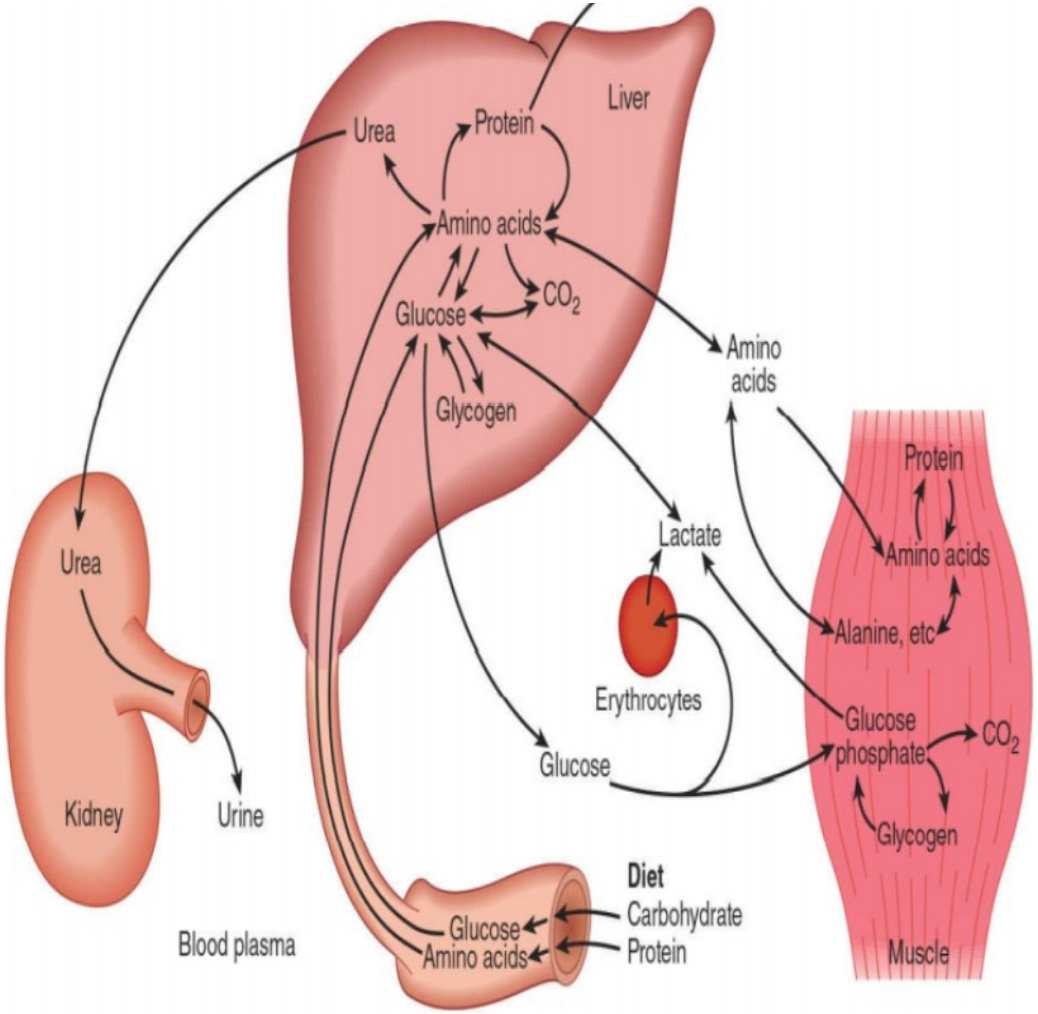
MCQS

- **Compartmentation is a Metabolic Regulation mechanism**

of the Major Pathways of Metabolism for example ----,---,and,---- enzymes mainly present in cytosol

However , TCA enzymes and ----- mainly active in ------

Glucose Homeostasis



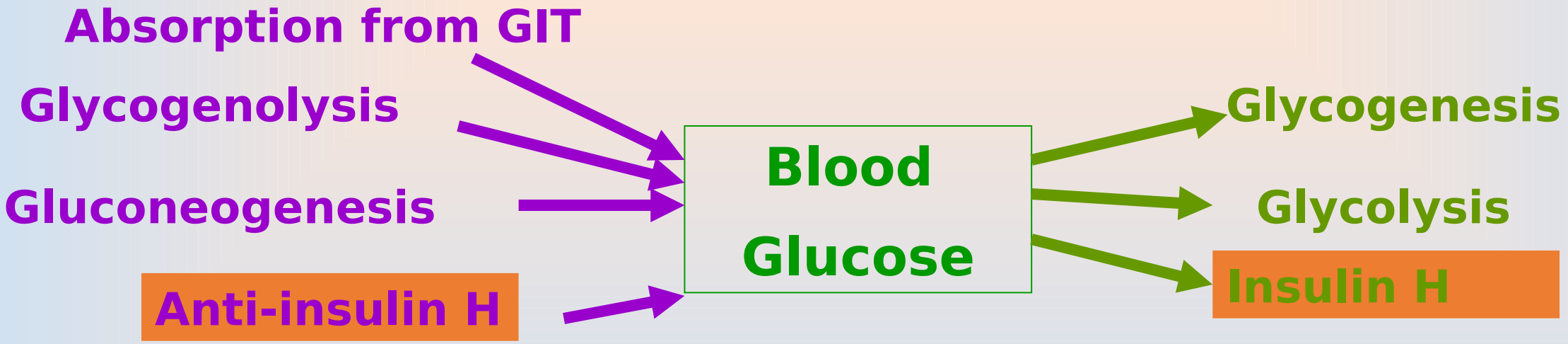
Blood Glucose

Normal Fasting blood glucose = 70-110 mg%

Normoglycemia: blood glucose within normal range

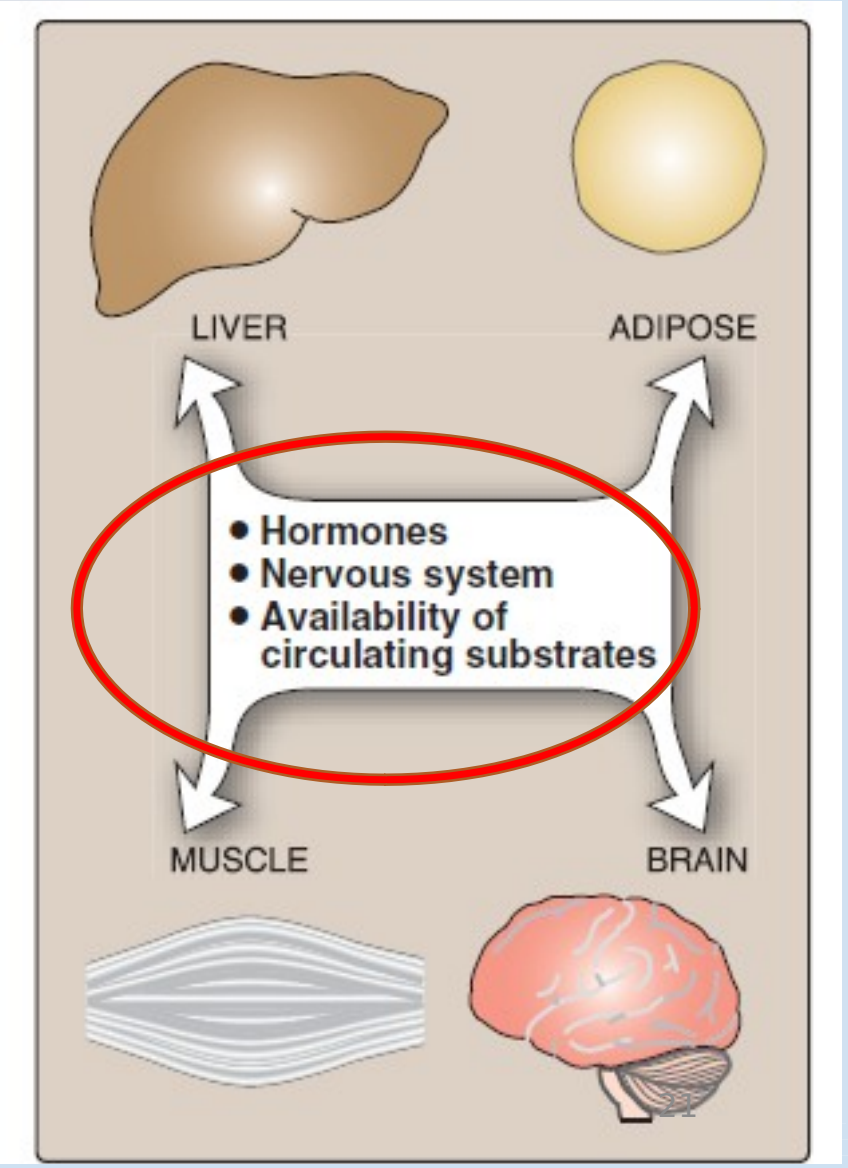
Hyperglycemia: blood glucose above normal range

Hypoglycemia: blood glucose below normal range



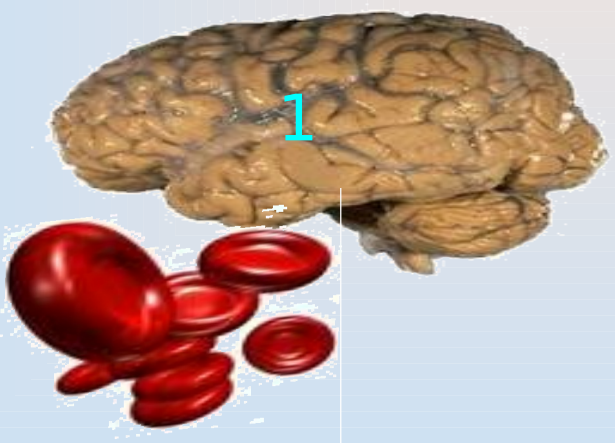
Four major organs play a dominant role in fuel metabolism

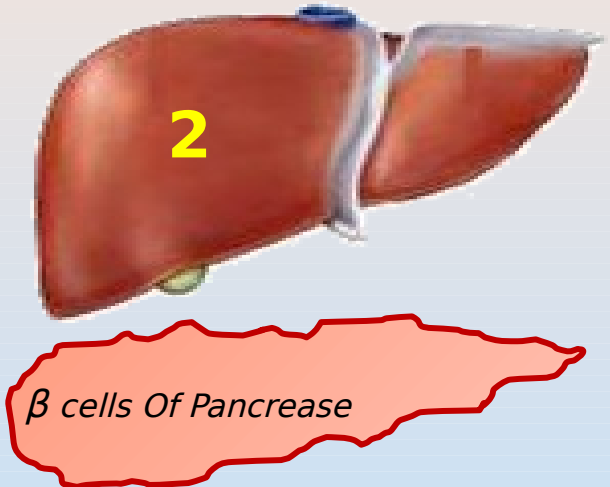
- Each organ is specialized for storage, use, or generation of specific fuels.
- Tissues don’t function in isolation, but rather form part of a network that require communication through…



Glucose Transporters

- $GLUT_1$: Brain and RBCs (Insulin-independent).
- $GLUT_2$: Hepatocytes , β-cells of pancreas, intestine (Insulin-independent).
- $GLUT_3$: Brain (Insulin-independent).
- $GLUT_4$: Adipose tissue, Heart and Muscles (insulin dependent)
- $GLUT_5$:Intestinal epithelium (Insulin-independent).





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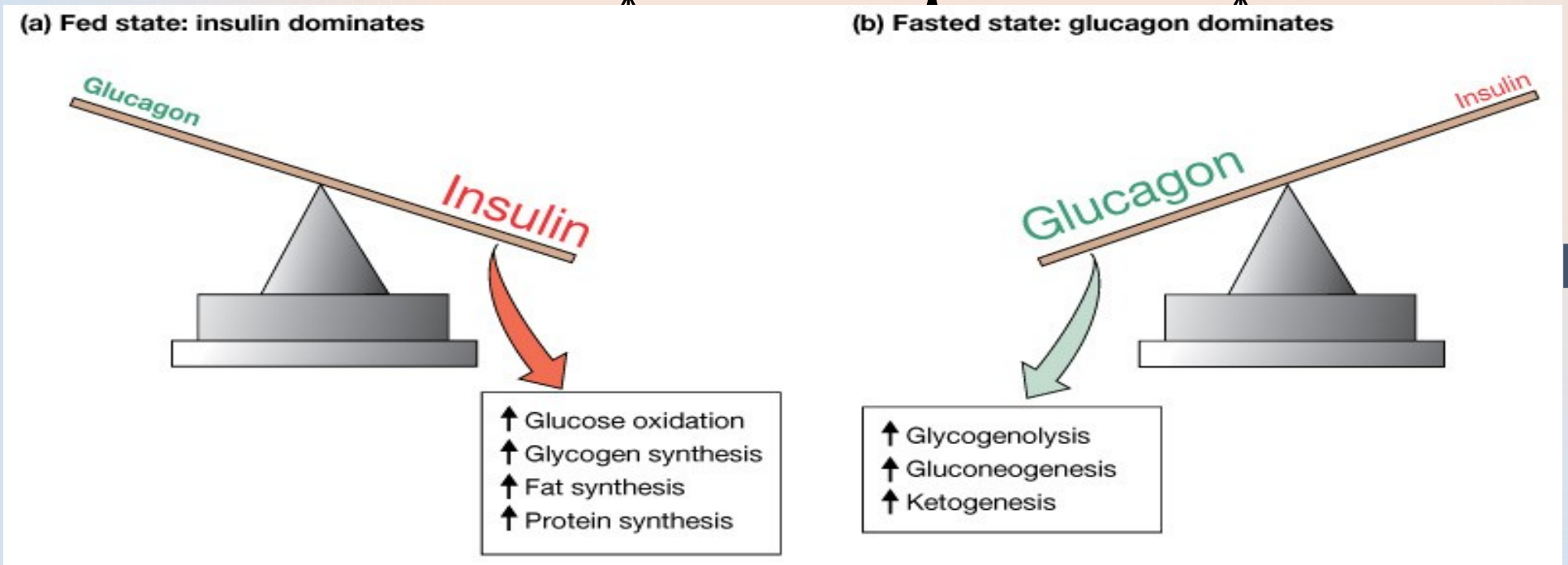
- **Sources of Blood Glucose**
- **1----**
- **2----**
- **3----**

Endocrine Regulation Of Metabolism

Endocrine Regulation Of Metabolism

Integration of metabolism is controlled 1ry by hormones as:

Insulin & glucagon, with Catecholamines playing a supporting role



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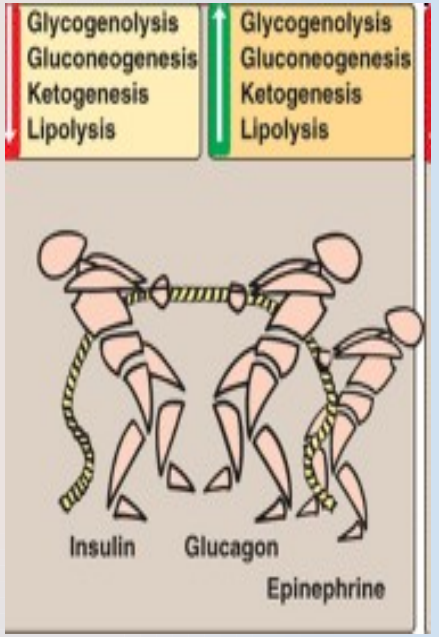
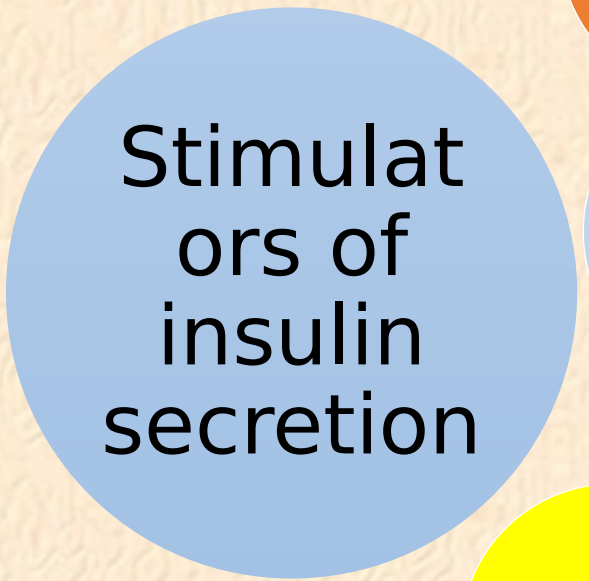


Anti-insulin hormones

1. **α-Cells of pancreas : Glucagon**
2. **Adrenal medulla : Epinephrine.**
3. **Adrenal cortex : corticosteroides**
4. **Anterior pituitary homones:**
    * **ACTH**
    * **TSH**
    * **Growth hormone.**

All theses hormones released in response to hypoglycemia

Stimulation of insulin secretion



Glucose: The most important stimulus for insulin secretion

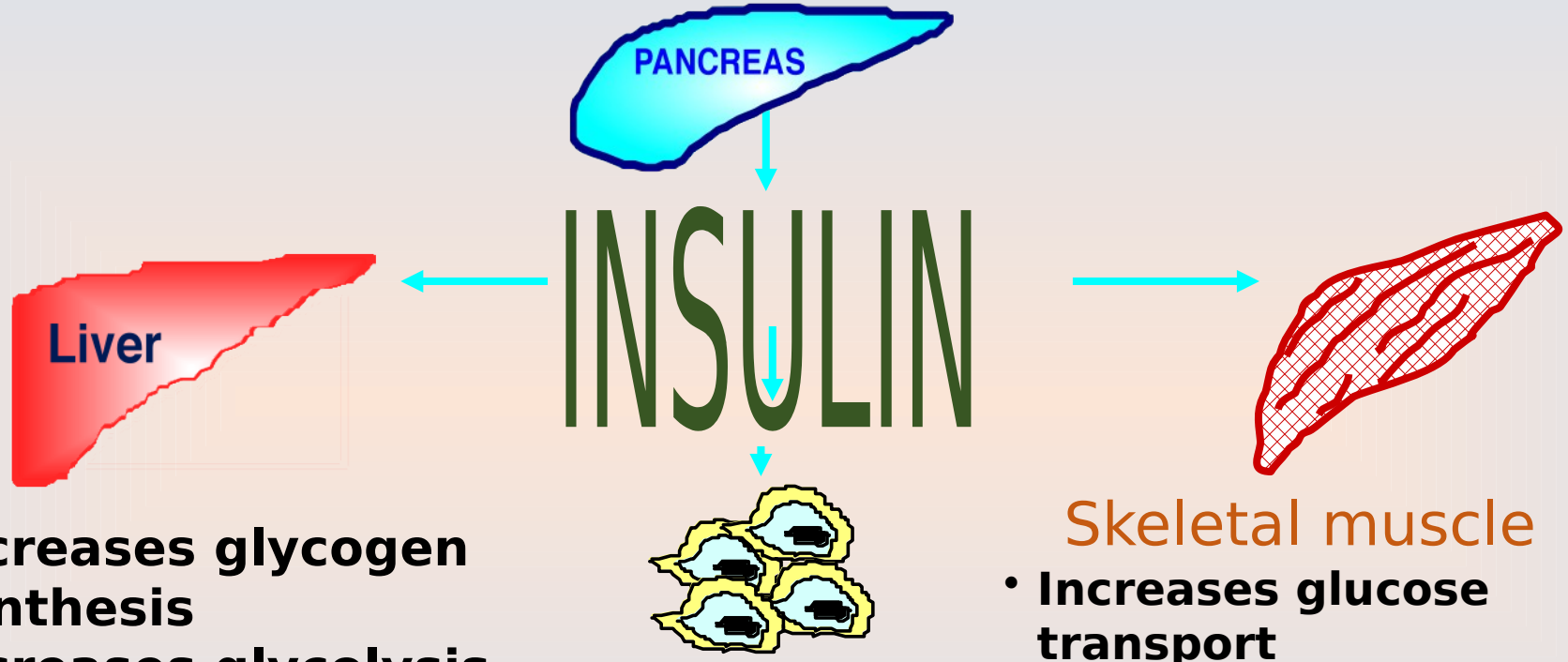
Amino acids

Gastrointestinal hormones

(Cholecystokinin)

Metabolic effect of insulin

Has hypoglycemic effect

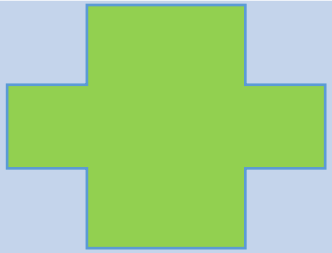


- **Increases glycogen synthesis**
- **Increases glycolysis**
- **Inhibits gluconeogenesis**

- **Increases glucose transport**
- **Increases lipogenesis**
- **Inhibits lipolysis**

- **Increases glucose transport**
- **Increases glycogen synthesis**

Regulation of glucagon secretion



Stimulation

1) Low blood glucose

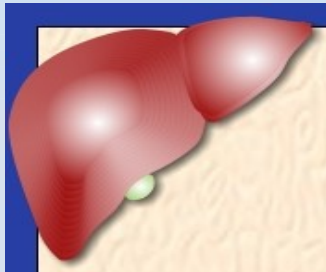
2) Dietary Amino Acids.

3) Elevated levels of circulating epinephrine and norepinephrine in stress, trauma or

Inhibition

Elevated blood glucose and by insulin

Metabolic effect of glucagon

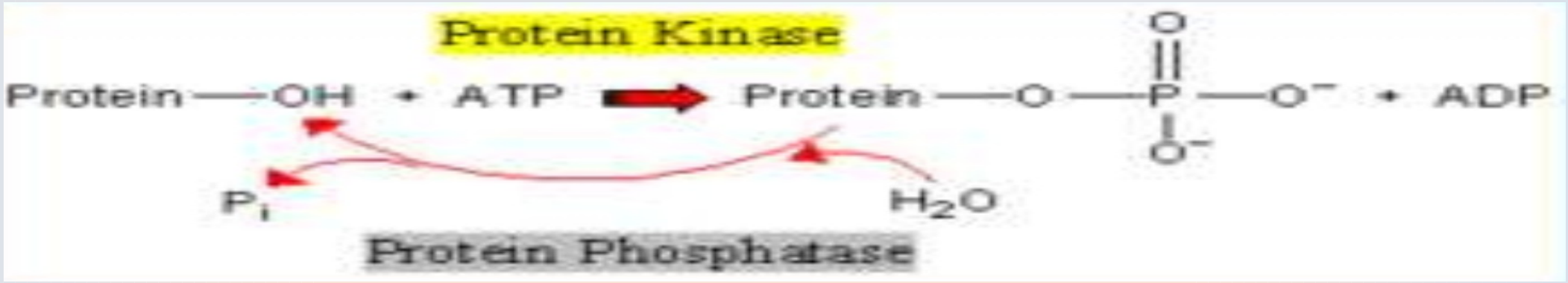


Carbohydrate metabolism

Lipid metabolism

Protein metabolism

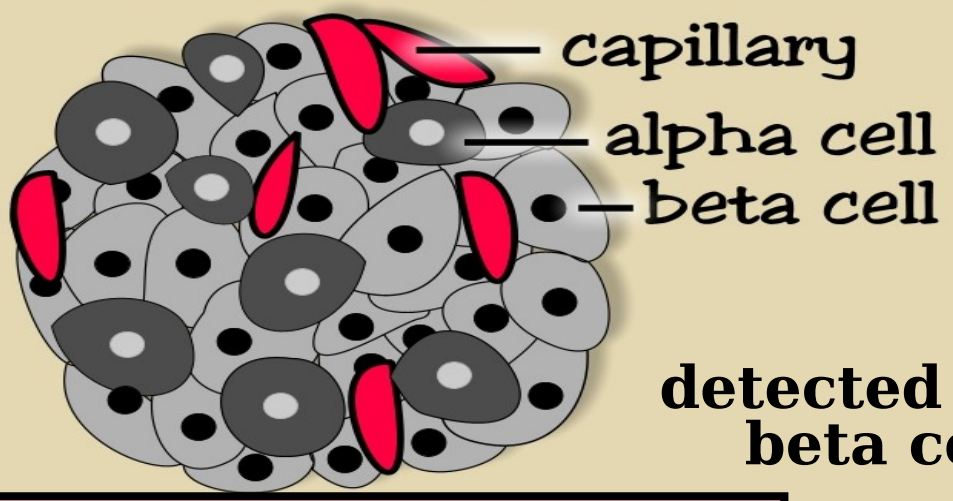
Covalent modification of enzymes



- **Many enzymes are regulated by addition or removal of phosphate groups to enzyme**
- **In fed state, insulin activate enzymes in the dephosyrelated form.**
- **In fast state, glucagon activate enzymes in the phosyrelated form.**

Effects of Insulin and Glucagon

Pancreatic Islet



Dual Hormonal Control achieves Glucose Homeostasis

Fall in blood glucose level

1

detected by the alpha cells

2

glucagon secretion

3

Glycogen to glucose

4

non-carbohydrates to glucose

liver

5

release of fatty acids from adipose tissue

fat cell

Rise in blood glucose level

1

detected by the beta cells

2

insulin secretion

Glucose to glycogen

3

liver

4

increased permeability of body cells to glucose

5

uptake of glucose for fatty acid synthesis

fat cell

body cell

NEXT

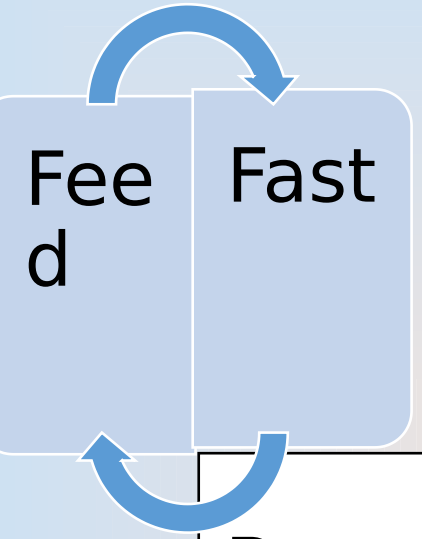
MCQS

- **In fed state, -----activate enzymes in the dephosyrelated form.**

- **In fast state, -----activate enzymes in the ----- form.**

Overview of the

- **Post Absorptive State**
- **Fasting state**



Post Absorptive state
Overnight fast after a meal

Fast lasting 12-24 Hours

Post absorptive state after a meal

Early fasting state during the night

(> 4 hrs from last meal).

Fast lasting > 3days

Prolonged Starvation

Prolonged starvation

Refed state

Overview of the Post Absorptive State

The post absorptive (well fed) state

- **2 to 4 hrs** after ingestion of a normal meal
- Transient ↑ in plasma glucose, AAs, & TAG.
- ↑ I/G ratio
- all tissues fuel, **Use glucose** as a fuel in liver, adipose tissue, muscle, and brain.
- Anabolic period (TAG glycogen to replenish fuel stores)
- protein synthesis

Fasting state

(> 4 hrs from last meal)

↓ Plasma levels of glucose,AAs,TAG

↓ I/G ratio with

Increase release of epinephrine

Catabolic period (degradation of TAG, glycogen, & protein)

Need to maintain adequate plasma levels of Glu to sustain energy to brain, RBCs & other Glu requiring tissues

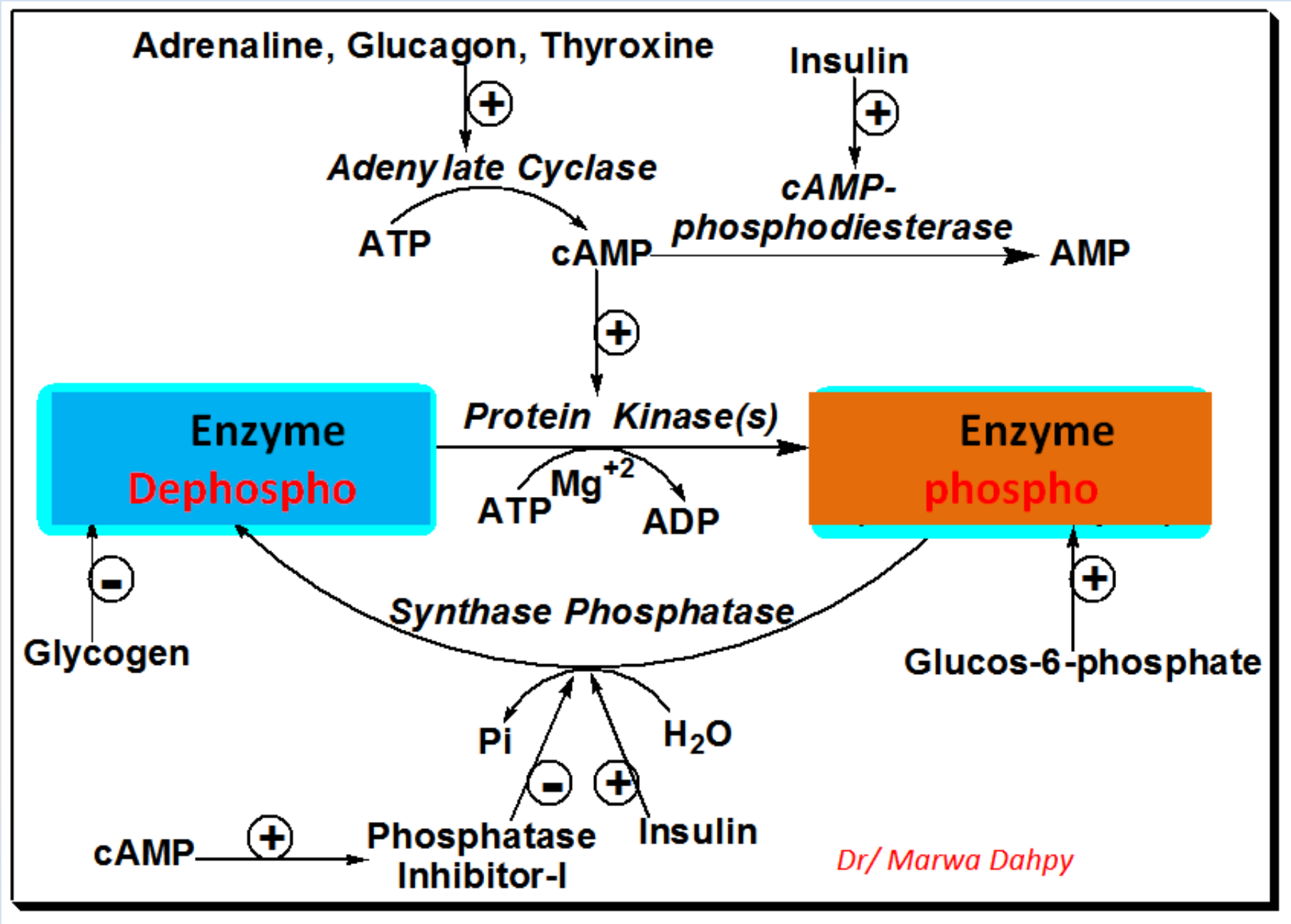
glucose Production from liver by gluconeogenesis

FAs Mobilization from adipose tissue

Synthesis & release of KBs from liver

The metabolic changes observed in fasting are generally opposite to those described for the well-fed state

Fed state	***Fasting***
• **Most of the enzymes regulated by covalent modification are dephosphorylated and active**	• **Enzymes are phosphorylated and active.** • ***glycogen phosphorylase*** • ***glycogen phosphorylase kinase*** • ***Hormone-sensitive lipase***


Adrenaline, Glucagon, Thyroxine
Insulin
Adenylate Cyclase
cAMP-phosphodiesterase
ATP
cAMP
AMP
Enzyme Dephospho
Protein Kinase(s)
Mg+2
ATP
ADP
Enzyme phospho
Synthase Phosphatase
Glycogen
Glucos-6-phosphate
Pi
H2O
cAMP
Phosphatase Inhibitor-I
Insulin
Dr/ Marwa Dahpy

Lecture Quiz

Insulin will activate one of the following enzymes:

a. phosphoenol-pyruvate carboxykinase
b. HMG CoA lyase
c. lipoprotein lipase
d. hormone-sensitive lipase

What happens 24 hours after a ?meal

a) Gluconeogenesis in the liver is the major source of blood glucose
b) Muscle glycolysis provides glucose to the blood.
c) Muscles convert amino acids to blood glucose.
d) Fatty acids released from adipose tissue provide carbon for synthesis of glucose.
e) Ketone bodies provide carbon skeleton for gluconeogenesis.

SUGGESTED TEXTBOOKS

"Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R.Ferrier.

"Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W.Rodwell.

PRAY, EAT
SLEEP, REVISE
& REPEAT
Thank you
Dr.Marwa Dahpy